

Drug used in treatment of gonorrhoea and syphilis

Lecture-3-
Reproductive Block
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Gonorrhea

- It is a **sexually transmitted infection of epithelium**
- It is the second most frequently reported bacterial sexually transmitted infection after *Chlamydia trachomatis*
- Common among **homosexual men and heterosexuals**
- **Manifestation:**
 - ✓ Cervicitis
 - ✓ Urethritis
 - ✓ Proctitis
 - ✓ Conjunctivitis
 - ✓ Pharyngitis
- **Urogenital tract infections** are most common

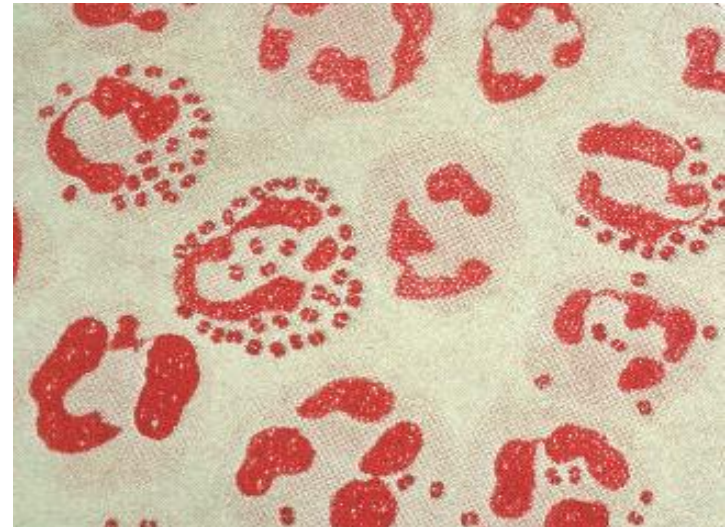
Gonorrhea

Sign & Symptoms:

- ✓ **Men** with gonorrhea may present with penile discharge and dysuria
- ✓ **Women** may present with mucopurulent discharge or pelvic pain; however, women often are asymptomatic
- ✓ **Neonatal** infections include conjunctivitis and scalp abscesses
- Untreated infections may lead to pelvic inflammatory disease (PID), disseminated gonococcal infections such as **arthritis**, and, although rare, **endocarditis** or **meningitis**
- Women who have had three or more episodes of PID develop infertility
- Factor aids transmission is that up to 35% women and 1-3% of men will be asymptomatics

Gonorrhea

- Causative pathogen:
 - ✓ *Neisseria gonorrhoea*, gram-negative bacteria
- Co-infection with *Chlamydia* has been reported in 20-40% of cases



Treatment of Gonorrhea

- Single dose regimens of third generation cephalosporin currently is the mainstay of therapy in treating **uncomplicated** cervical, urethral, anorectal, and pharyngeal infections
- Ceftriaxone, 250 mg IM injection, single dose
Or Cefixime 400 mg orally, single dose
- **In case of allergy to cephalosporin:**
Azithromycin, 2 g orally, single dose

Treatment of Gonorrhea

- Co-infection with ***Chlamydia*** occurs frequently, initial treatment regimens must also incorporate an agent that is effective against Chlamydial infection:
 - ❑ Azithromycin 1gm PO, single dose
 - ❑ Or Doxycycline 100 mg PO bid for 7 days
- **Pregnant women** with gonorrhea should not take doxycycline, she should receive concurrent treatment with macrolide antibiotics for possible Chlamydia infection

Disseminated Gonorrhea treatment

- **Parenteral therapy** is continued for 24-48 hr after sign of improvement are seen
- Followed by **oral therapy** to complete a full week's course
- If **meningitis** is present, ceftriaxone is continue parenterally for up to **2 weeks**
- If **endocarditis** is present the drug should be taken for at least **4 weeks**

Gonorrhea resistance to antimicrobial agents

- *N. Gonorrhoeae* has become resistance to numerous antibiotics such as:

- ☐ Sulfonamides
- ☐ Penicillin
- ☐ Tetracyclines, such as doxycycline
- ☐ Fluroquinolones
- ☐ Spectinomycin



Gonorrhea resistance to antimicrobial agents

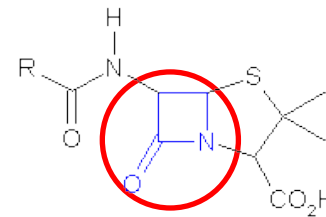
- ✓ **Fluoroquinolones** are not recommended for treatment of gonorrhea or associated conditions because of the emergence of quinolone-resistant *N. Gonorrhoeae*
- ✓ Although **doxycycline** is an alternative regimen in combination with a cephalosporin, azithromycin is preferred because of the high prevalence of tetracycline resistance
- ✓ **Spectinomycin** can be reserved for use against multiresistant strains
- ✓ **3rd generation cephalosporin** remained highly effective as a single dose therapy for gonorrhea

Gonorrhea

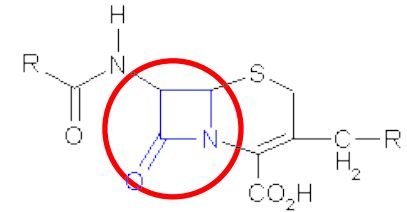
- Treatment of sexually acquired reactive arthritis includes:
 - ✓ Rest with restriction of physical activity
 - ✓ Physical therapy to prevent muscle wasting
 - ✓ Cold compresses
 - ✓ Nonsteroidal anti-inflammatory drugs
 - ✓ Antimicrobial therapy for three months or longer

Cephalosporin

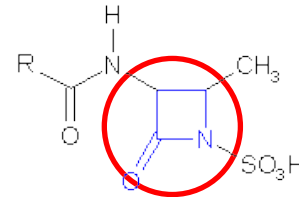
- They selectively interfere with synthesis of the bacterial cell wall
- They are semisynthetic AB with **β -lactam ring** related to penicillins
- Have ***wider spectrum of activity than penicillins***
- **β -lactam antibiotics** are named after the β -lactam ring that is essential to their activity



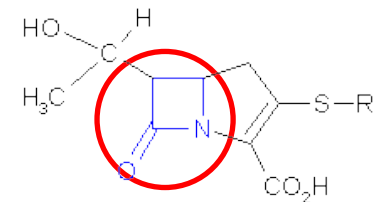
Penicillin nucleus



Cephalosporin nucleus



Monobactam nucleus

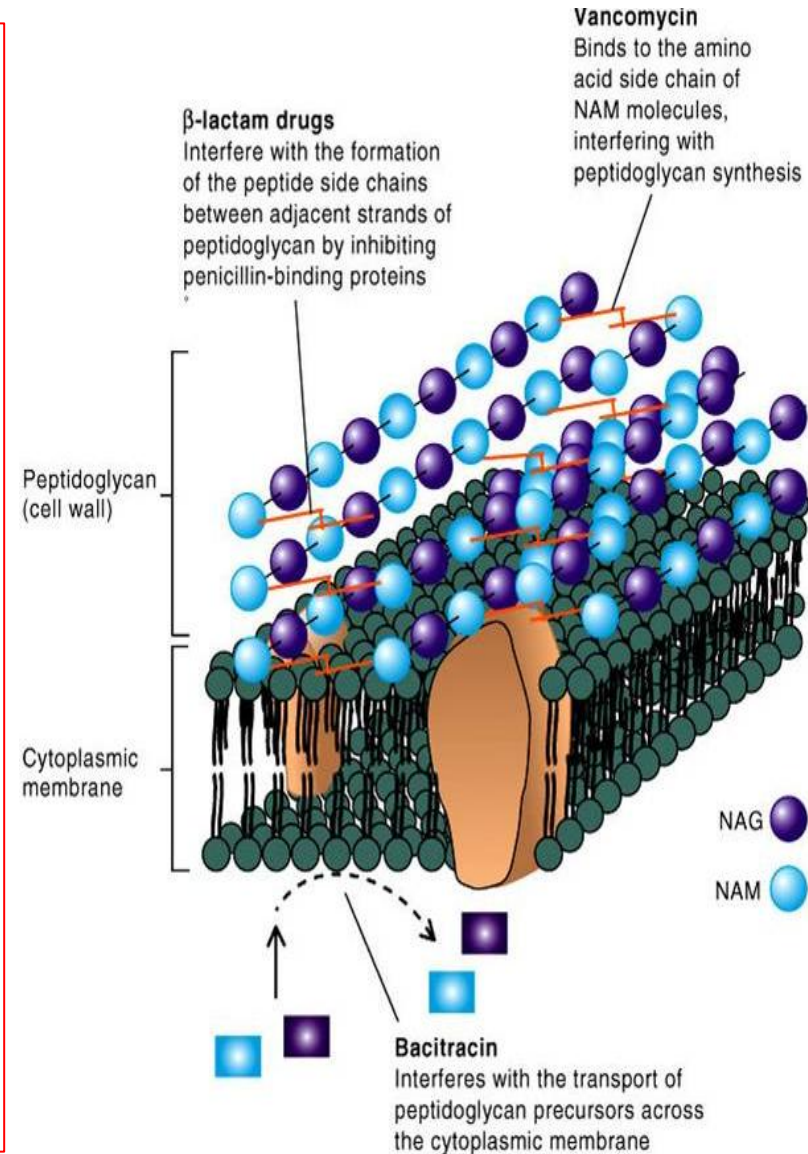


Carbapenem nucleus

Cephalosporin

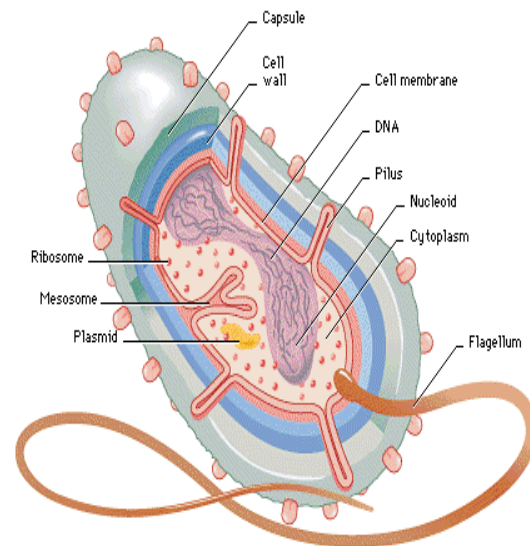
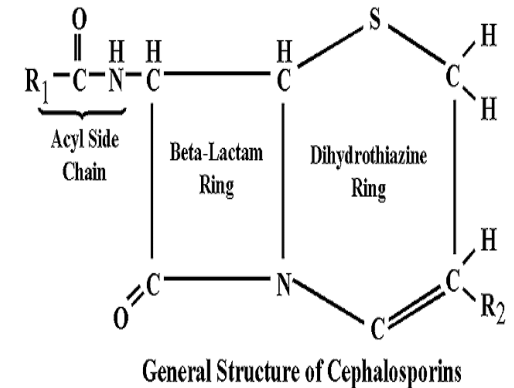
MOA:

- The rigid cell wall of the bacteria **protects** the bacteria from lysis (or breaking)
- So, Cell wall is essential for the **survival** of bacteria
- The cell wall is composed of a polymer called **peptidoglycan** that consists of **glycan** units joined to each other by **peptide cross-links**, which gives rigidity of the cell wall
- The synthesis of peptidoglycan requires enzyme called **transpeptidase**
- Cell wall inhibitors AB **inhibit transpeptidase**
- **Result** in formation of bacteria with **weak cell wall** → bacteria undergo **lysis**
- They are **bactericidal**



Cephalosporin

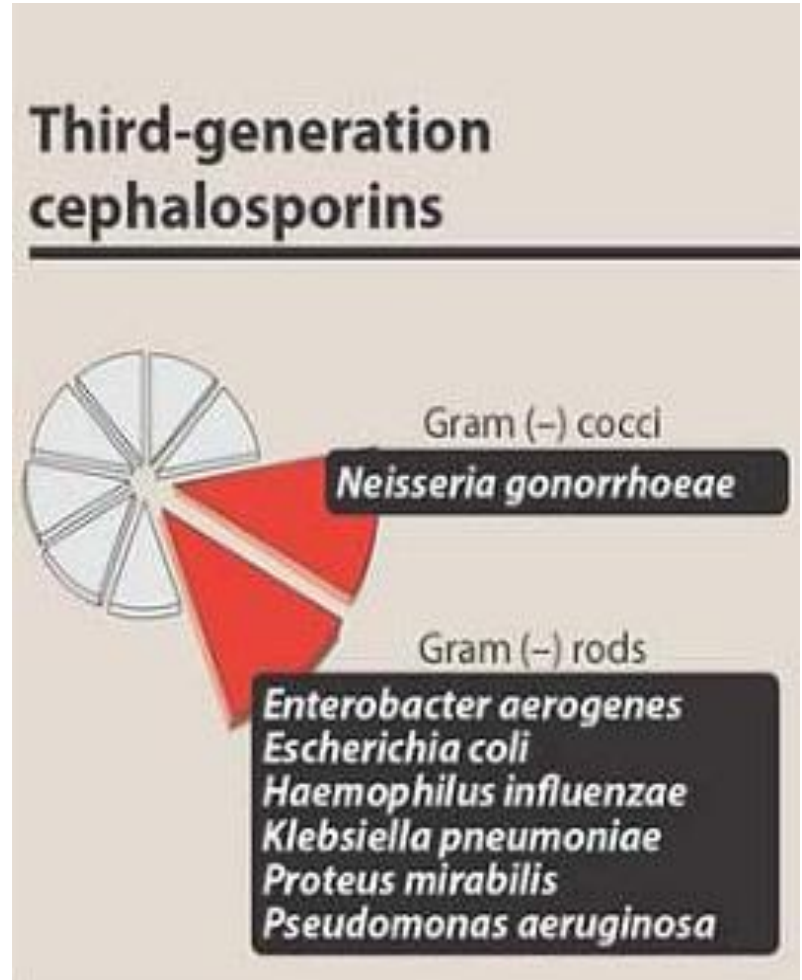
- Cephalosporins have been **classified** based largely on their **bacterial susceptibility patterns** and **resistance to β -lactamases** in to **4 generations**
- In general, progression from the 1st generation to the 4th generation drugs shows an increase in the sensitivity of **gram-negative** microorganisms and decrease in the sensitivity of **gram-positive** microorganism



3rd Generation Cephalosporin

Parenteral	Oral
-Cefotaxime -Ceftazidime -Ceftriaxone -Ceftizoxime	-Ceftixime

- ✓ Have enhanced activity against **gram-ve** bacilli



Adverse effect of Cephalosporin

1. Pseudomembranous colitis (diarrhea)
2. Nephrotoxicity
3. Hypersensitivity (allergic reaction):
 - ☐ Patients who have had an **anaphylactic** response to **penicillins** **should not** receive **cephalosporins**
 - ☐ about 8-10 % show **cross-sensitivity**
 - ☐ The rate of highest allergic cross sensitivity is b/w penicillin and 1st generation cephalosporins
4. Ceftriaxone is now contraindicated in **newborns** receiving concurrent administration of **calcium containing solution** or product due to risk of **fatal precipitation in lung and kidney**



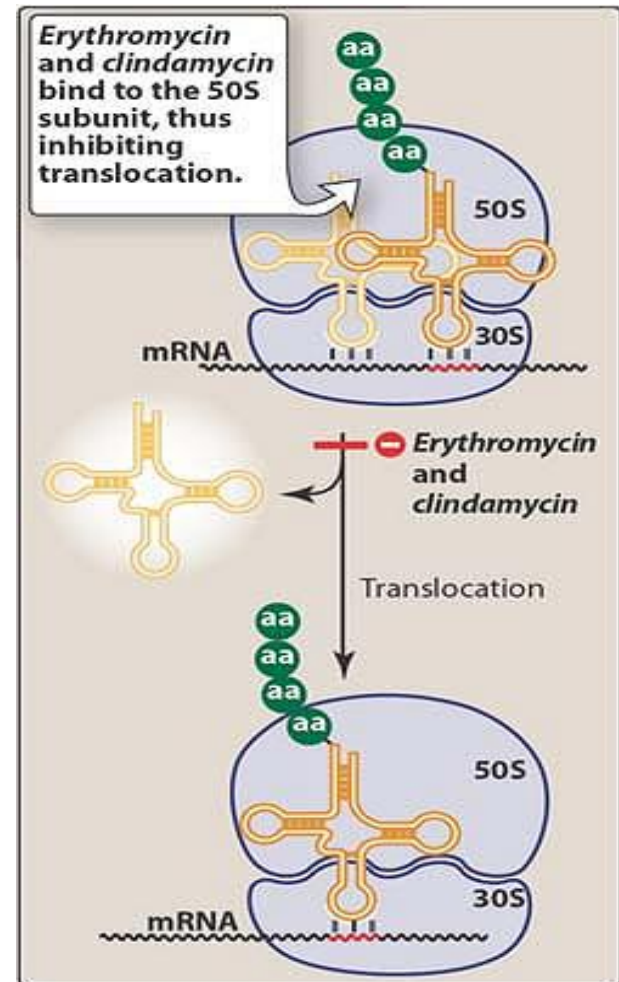
Macrolides

E.g., Clarithromycin, Azithromycin, Erythromycin

MOA:

- The macrolides bind **irreversibly** to a site on the 50S subunit of the bacterial ribosome, thus inhibiting bacterial protein synthesis

- ✓ They are generally considered **bacteriostatic**, they may be bactericidal at higher conc



Macrolides

- Directed mainly against **gram-positive** and few **gram-negative** organisms, like:
 - ✓ *Streptococci, Pneumococci, Staphylococci, Gonococci, Mycoplasma, Chlamydia, Corynebacterium diphtheriae* and some atypical *Mycobacteria*
- *It is suitable as a substitute in allergy or resistance to penicillin*
- They can be given **orally**



Uses of Macrolides

- Atypical pneumonia
- Whooping cough
- Streptococcal infections
- Staphylococcal infection
- Diphtheria
- **Syphilis and gonorrhea**
- Tetanus
- Anthrax
- Skin infections
- Acne
- H. Pylori peptic ulcer



Macrolides

- Adverse effects:

1. **Hepatitis**
2. **GI upset:** Nausea, vomiting, abdominal pain, diarrhea



GI disturbance

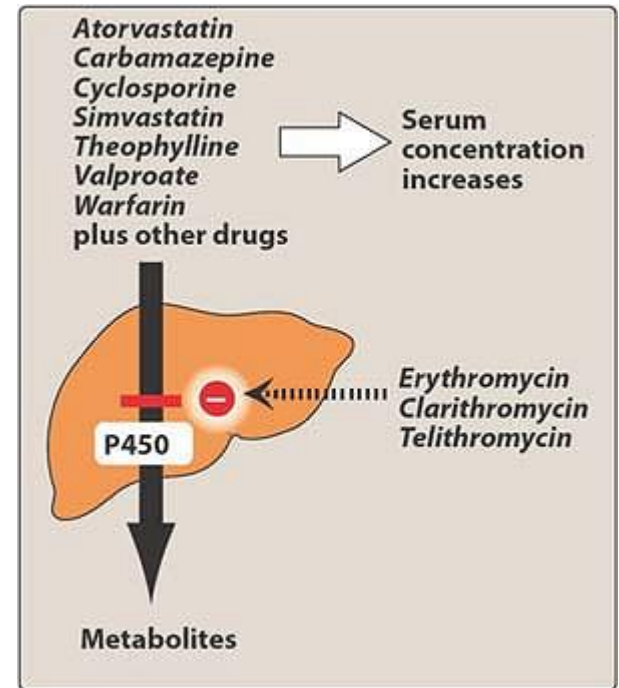


Jaundice

Some adverse effects of
macrolide antibiotics

Macrolides

- Drug interaction:
- ✓ They inhibit the CYP450 enzymes, inhibit metabolism of many drugs in the liver
- ✓ They raise the plasma levels of warfarin, digoxin...etc



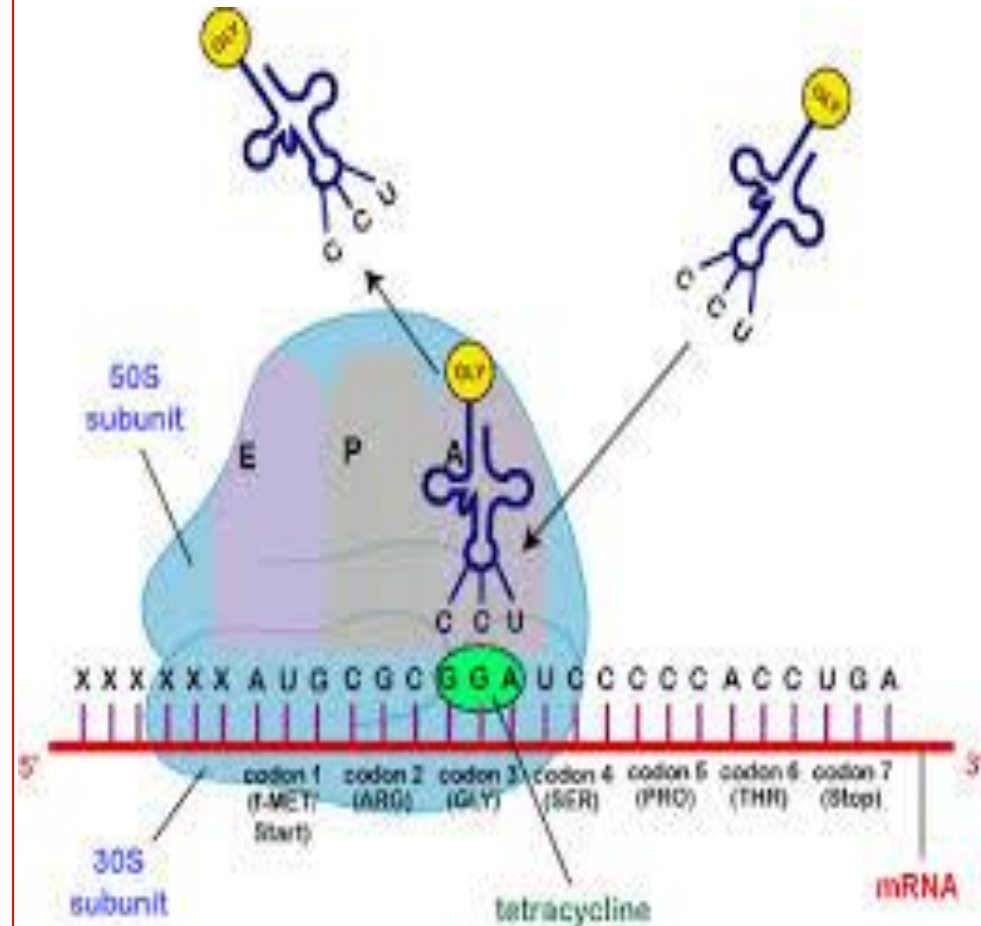
Inhibition of the cytochrome P450 system by erythromycin, and clarithromycin

Tetracyclines

E.g, Doxycycline , Tetracycline

MOA:

- They are taken up by the microorganism by **active transport**
- They **bind to 30S ribosome** and prevent protein synthesis
- ✓ They are **Bacteriostatic**



Tetracyclines

- ✓ They are **broad spectrum AB**:
 - Effective against **gram+ve** and **gram-ve** bacteria
 - Anaerobic bacteria
 - Rickettsiae
 - **Chlamydia**
 - Mycoplasma
 - Protozoa
- ✓ Tetracyclines are the drugs of choice for infections



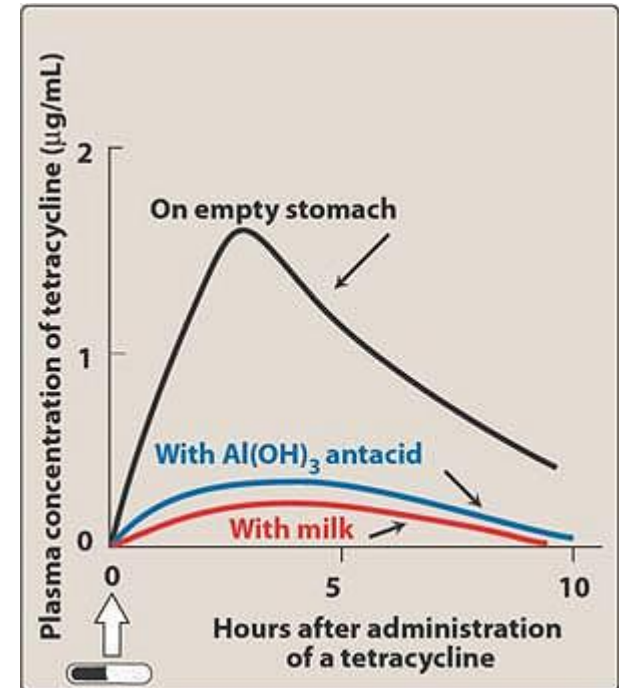
Tetracyclines

PK:

Absorption:

- All tetracyclines are **adequately but incompletely** absorbed after oral ingestion
- These drugs form nonabsorbable chelates with calcium and other divalent or trivalent cations, So their absorption may decrease with:
 - ✓ **Foods**, especially, **milk**
 - ✓ **Drugs**: Magnesium and aluminum **antacids** and in **iron** preparations

Note: This presents a problem if a patient self-treats the epigastric upsets caused by tetracycline ingestion with antacids



Effect of antacids and milk on the absorption of tetracyclines

Tetracyclines

PK:

Distribution:

- **Tetracycline concentrate in:**
 - ✓ **Liver**
 - ✓ **Kidney**
 - ✓ **Spleen**
 - ✓ **Skin**
 - ✓ **They bind to tissues** undergoing calcification , e.g, teeth and bones



Tetracyclines cause permanent staining of the teeth

Tetracyclines

Adverse effects:

1. **Gastric discomfort** (common)
2. **Deposition** in the bone and teeth
3. Fatal **hepatotoxicity** occur in pregnant women
4. **Phototoxicity**, dermatitis on exposure to sun
5. **Renal toxicity**

Contraindications:

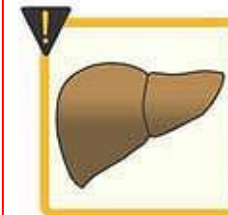
- ✓ **Pregnant or breast-feeding women**
- ✓ **Children < 8 y.o**



GI disturbance



Deposition of drug in bones and teeth



Liver failure



Phototoxicity



Vertigo



Avoid in pregnancy

Some adverse effects of *tetracycline*

Uses of Tetracyclines

Drug of Choice

1. Rickettsial infection
2. **Chlamydial infection**
3. Atypical pneumonia due to *Mycoplasma pneumoniae*
4. Cholera
5. Brucellosis
6. Plague

Other uses

1. Traveller diarrhea
2. Acne
3. **Sexually transmitted diseases such as syphilis and gonorrhea**
4. Protozoal infection: Amebiasis, and Malaria



Infection	Recommended regimen
Adults Uncomplicated urethral, cervical, or rectal gonococcal infection	Ceftriaxone 250 mg IM in a single dose <i>plus</i> Azithromycin 1 g orally in a single dose, or doxycycline, 100 mg orally twice per day for 7 days If ceftriaxone is not available, use cefixime 400 mg orally in a single dose <i>plus</i> Azithromycin, 1 g orally in a single dose, or doxycycline, 100 mg orally twice per day for 7 days <i>plus</i> Test of cure in one week For patients with severe cephalosporin allergy, use azithromycin, 2 g orally in a single dose <i>plus</i> Test of cure in one week

<i>Infection</i>	<i>Recommended regimen</i>
Adults Disseminated gonococcal infection (hospitalization recommended)	Ceftriaxone 1 g IM or IV every 24 hours until 24 to 48 hours after improvement begins <i>or</i> Cefotaxime 1 g IV every 8 hours until 24 to 48 hours after improvement begins <i>or</i> Ceftizoxime 1 g IV every 8 hours until 24 to 48 hours after improvement begins 24 to 48 hours after improvement begins, switch to cefixime, 400 mg orally twice per day, for at least one week of total antimicrobial treatment
Gonococcal conjunctivitis	Ceftriaxone, 1 g IM in a single dose
Gonococcal meningitis and endocarditis	Ceftriaxone, 1 to 2 g IV every 12 hours for 10 to 14 days for meningitis and at least 4 weeks for endocarditis

<i>Infection</i>	<i>Recommended regimen</i>
Adults Pharyngeal gonococcal infection	Ceftriaxone, 250 mg IM in a single dose <i>plus</i> Azithromycin, 1 g orally in a single dose, or doxycycline, 100 mg orally twice per day for 7 days
Pregnant patients	Ceftriaxone, 250 mg IM in a single dose For patients with penicillin allergy, use azithromycin, 2 g orally in a single dose
Children Urethral, cervical, rectal, or pharyngeal gonococcal infection	Children weighing > 45 kg (100 lb): same as adult recommendations Children weighing ≤ 45 kg: ceftriaxone, 125 mg IM in a single dose
Bacteremia or arthritis	Children weighing > 45 kg: ceftriaxone, 50 mg per kg IV or IM per day for 7 days Children weighing ≤ 45 kg: ceftriaxone, 50 mg per kg IV or IM per day (not to exceed 1 g per day) for 7 days

<i>Infection</i>	<i>Recommended regimen</i>
Neonates Infants born to mother with untreated gonorrhea with no signs of infection	Ceftriaxone, 25 to 50 mg per kg IV or IM in a single dose, not to exceed 125 mg
Neonatal disseminated gonococcal infection or scalp abscess	Ceftriaxone, 25 to 50 mg per kg IV or IM per day for 7 days <i>or</i> Cefotaxime, 25 mg per kg IV or IM every 12 hours for 7 days
Neonatal meningitis	Ceftriaxone, 25 to 50 mg per kg IV or IM per day for 10 to 14 days <i>or</i> Cefotaxime, 25 mg per kg IV or IM every 12 hours for 10 to 14 days
Ophthalmia neonatorum	Ceftriaxone, 25 to 50 mg per kg IV or IM in a single dose, not to exceed 125 mg

Syphilis

- Syphilis is a chronic systemic infection, is usually sexually transmitted and is characterized by episodes of active diseases interrupted by periods of latency
- Causative organism:
 - ✓ *Treponema pallidum*
- It cause localized infection at the site of invasion result in local lesion, and then the organism disseminates throughout the body
- Late complication are due to chronic inflammatory reaction that continues over many years (cardiovascular syphilis, neurosyphilis)

Stages of Syphilis

Stage	Characteristics
Primary syphilis	Typically presents as a solitary, painless chancre
Secondary syphilis	Can have a wide variety of symptoms, especially fever, lymphadenopathy, rash, and genital or perineal condyloma latum
Latent syphilis	All clinical manifestations subside, and infection is apparent only on serologic testing
Late or tertiary syphilis	Can manifest years after infection as gummatous disease, cardiovascular disease, or central nervous system involvement
Neurosyphilis (can develop in any stage of syphilis)	Seizures, ataxia, aphasia, personality change, visual disturbance, hearing loss, neuropathy, loss of bowel or bladder function

Syphilis

- **Treatment goals:**

- ✓ Eliminate the infection
- ✓ Prevent onward spread
- ✓ Prevent complication

- Treatment choice are predicated on:

- ☐ Convenience of dosage
- ☐ CSF penetration
- ☐ Concomitant HIV infection
- ☐ Allergy

- **Penicillin** remains the mainstay of treatment, despite widespread use of penicillin

- The treatment of syphilis is similar in **HIV-positive** and **HIV-negative** patients
- *However, HIV-positive patients who develop syphilis are at higher risk for treatment failure and neurosyphilis*

Treatment of Syphilis

- The treatment plan for syphilis remains relatively unchanged in recent years and continues to vary with stage of infection
- **Benzathine penicillin** is convenient to use and is consequently a popular choice in many parts of the world; however, it has poor CSF penetration
- Some experts consider that **procaine penicillin** is a better choice, particularly when used with **probenecid**, *which delays renal excretion and prolongs the half-life of penicillin in the blood*

Primarily, secondary or early latent syphilis if the CSF is negative

- **Benzathine penicillin G** 2.4 million units IM as a **single dose**
- Alternative: **procaine penicillin** 600 mg IM daily for 10 days + **probenecid** 10 mg twice daily
- If patient is allergic to penicillin:
 - ✓ **Doxycycline** 100 mg orally twice a day for 2 weeks
 - ✓ Or **Tetracycline**, 500 mg orally four times daily for 2 weeks

Late latent, Tertiary Syphilis

- **Benzathine penicillin G** 2.4 million units may be given at weekly intervals for 3 weeks
- **Alternative:**
 - ✓ **Procaine penicillin** 1.8 gm IM daily + probenecid 500 mg four times a day for 17 days
- In case of allergy: **doxycycline** 100 mg PO twice a day for 28 days

Neurosypphilis

- Aqueous crystalline penicillin G, 18 to 24 million units daily administered as 3 to 4 million units intravenously every 4 hours for 10 to 14 days
or
- Penicillin G procaine, 2.4 million units intramuscularly once daily for 10 to 14 days *plus* Probenecid, 500 mg orally four times daily for 10 to 14 days
- Patient with confirmed penicillin allergy:
Desensitization and treat with penicillin

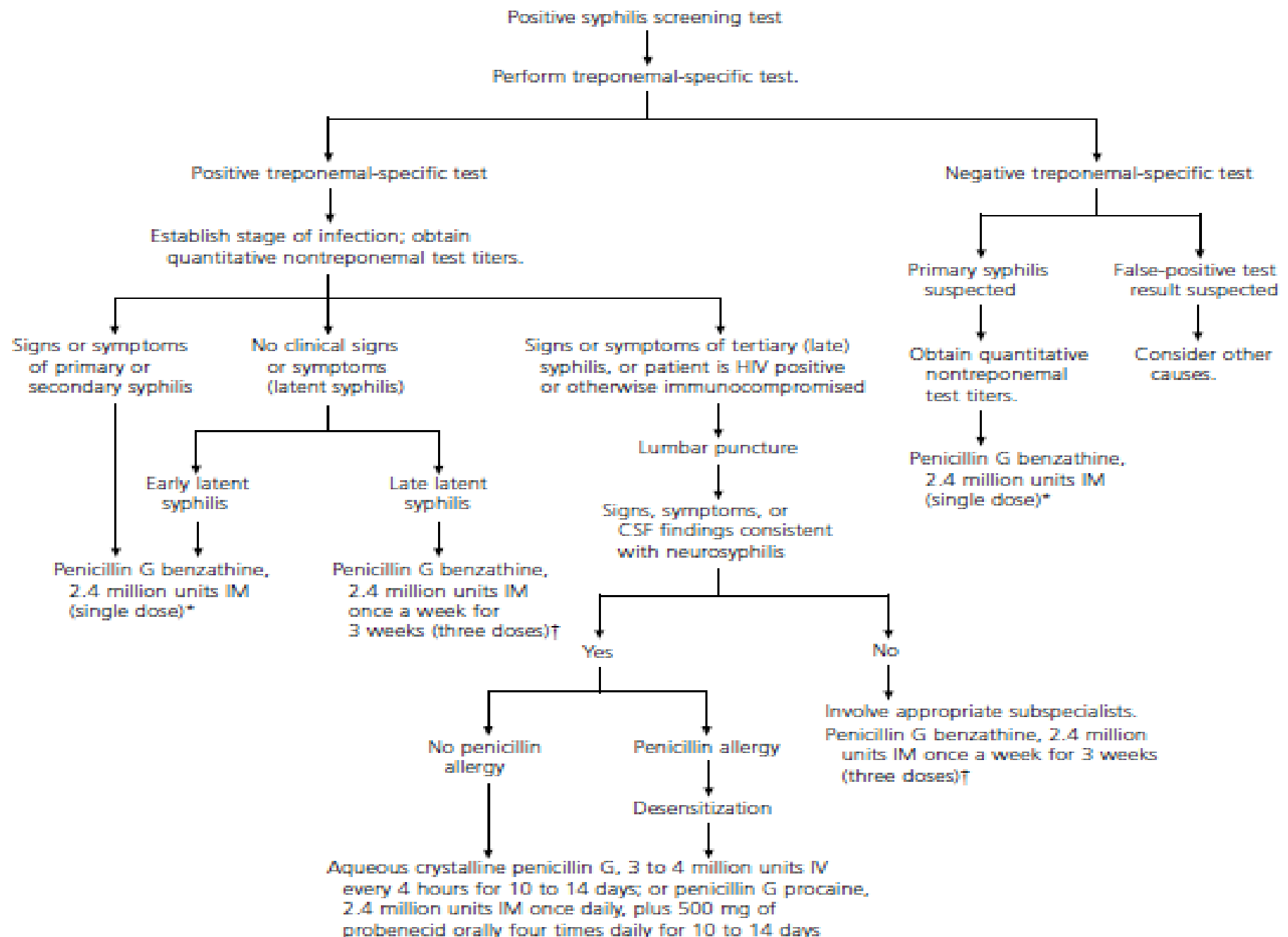
Syphilis in Pregnancy

- Penicillin is the only recommended agent for the treatment of syphilis in pregnancy
- Procain penicillin and benzathine penicillin are both suitable drugs for treatment in pregnancy
- Doxycycline is not recommended
- Patient with confirmed penicillin allergy:
Desensitization and treat with penicillin

Jarisch-Herxheimer reaction

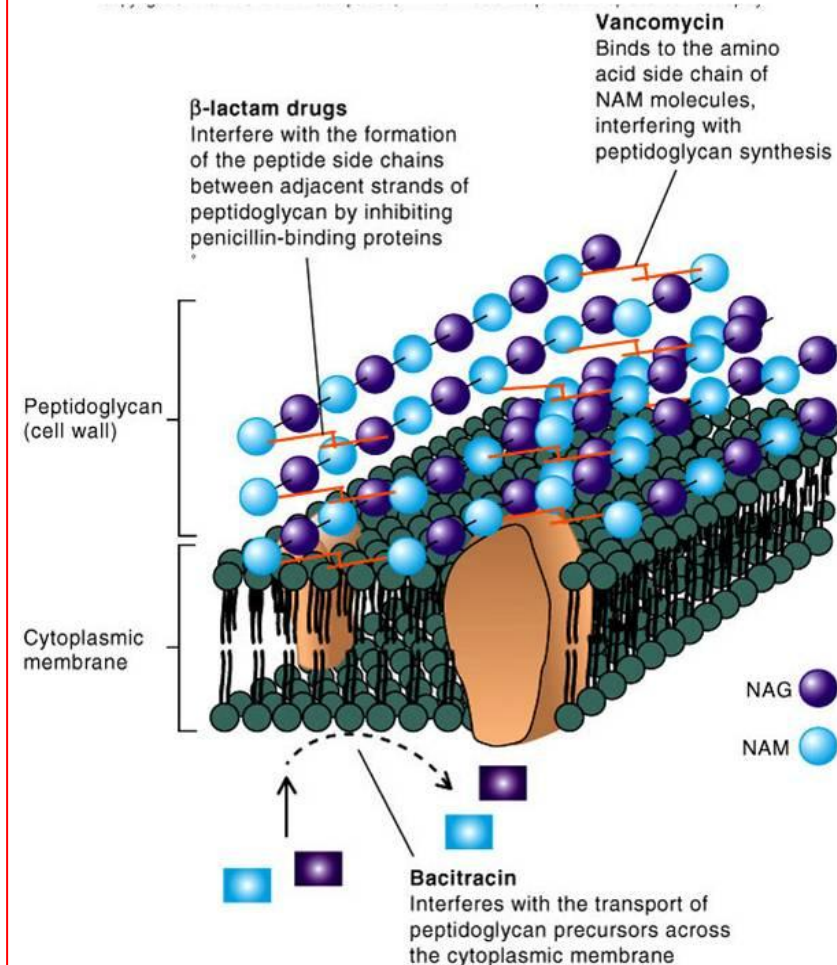
- Influenza like reaction with headache, myalgia and fever occurs within 24 hr of starting therapy
- Due to: massive lysis of the pathogen, spilling large quantities of inflammatory cytokines into the bloodstream
- Manage:
 - ✓ **Antipyretics**
 - ✓ **Systemic steroid**: prednisolone 30 mg daily for 3 days, commencing the day before treatment is said to be helpful

Treatment of Syphilis



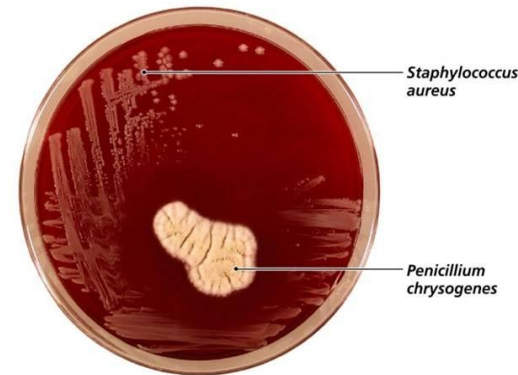
Penicillins

- Are ***the most widely effective*** AB
- They are Beta-lactam AB that inhibit bacterial cell wall
- Their mechanism of action is similar to cephalosporin
- The ***least toxic drugs*** known, but ↑resistance has limited their use



Penicillins

- The discovery of the first antibiotic was an accident:
- ✓ **Alexander Fleming** accidentally contaminated a plate with a fungus, *Penicillium notatum*
- ✓ He observed a clearly defined region of no bacterial growth where the fungi had contaminated the plate
- ✓ The area around the fungus was eventually referred to as a zone of inhibition



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Benzylpenicillin and its long acting parenteral forms

- Benzylpenicillin is the first naturally produced penicillin
- Also called Penicillin G
- It is poorly absorbed orally and must be given by injection
- Supply as highly soluble potassium or sodium salts for intramuscular or intravenous administration



Benzylpenicillin and its long acting parenteral forms

- The **plasma half life is short** and in order to prolong its effect benzylpenicillin was first mixed with **oils** or **waxes**, so that the release of penicillin from intramuscular injection sites was delayed
- Later, insoluble salts of penicillin were prepared that similarly act as **intramuscular depots** for the release of penicillin into the bloodstream
- Several repository penicillins are in use that are long acting forms that liberate benzylpenicillin:
 - ☐ Procain penicillin
 - ☐ Benzathine penicillin

Benzylpenicillin and its long acting parenteral forms

Benzathine Penicillin

- It is poorly absorbed in water
- Available as an IM preparation
- It has a **local anesthetic effect** comparable with that of procaine penicillin
- It is slowly absorbed after IM injection
- Yielding a vary low plasma conc.: a dose of 1.2 mega units produces mean plasma conc. of 0.1 mg/l 1week after injection, 0.02 mg/l after 2 weeks and 0.002 mg/l after 4 weeks

Benzylpenicillin and its long acting parenteral forms

Procaine Penicillin

- A poorly soluble in water
- Administered IM as a suspension of crystals which slowly dissolve at the site of injection
- An injection of 0.6 g yield a peak plasma conc. of 1-2 mg benzylpenicillin/l after 2-4hr
- Some side effect may be due to liberated procaine such as:
 - ✓ Acute anxiety
 - ✓ Hypertension
 - ✓ Tachycardia
 - ✓ Most sever (Convulsion, Cardiac arrest)

Antimicrobial activity of Benzylpenicillin

- In general, it is effective against mainly **gram+ve** (*streptococci, staphylococci*), effective against **gram-ve** microorganism to varies degree
- *Nisseria gonorrhoeae* and *Nisseria meningitidis* were initially highly susceptible to benzylpenicillin, but beta-lactamase producing strains of gonococci are now common

Uses of Benzylpenicillins

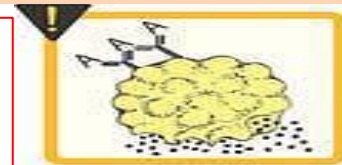
1. Pneumococcal infections: pneumonia, meningitis and osteomyelitis
2. Streptococcal Infection: Pharyngitis, sinusitis, pneumonia, meningitis and endocarditis
3. Meningococcal infections
4. Staphylococcal infections
5. Syphilis
6. Diphtheria
7. Anthrax
8. Anaerobic infections: abscesses
9. Tetanus and gas gangrene



Adverse effects of Benzylpenicillins

- Penicillins are among the safest drugs, and blood levels are not monitored
1. **Hypersensitivity:** incidence up to 5%, with manifestations ranging from skin rash to anaphylactic shock (in less than 0.05% of patients)
 2. Pseudomembranous colitis, diarrhea
 3. Massive IV doses of sodium and potassium salts can lead to severe electrolyte disturbance
 4. Nephritis
 5. Decrease coagulation
 6. **Neurotoxic effects:** mostly seizure

(Caution with intrathecal injections)



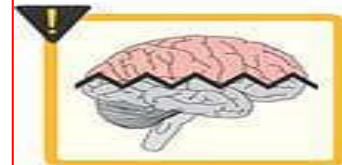
Hypersensitivity



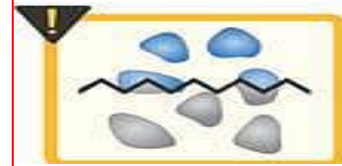
Diarrhea



Nephritis



Neurotoxicity



Hematologic toxicities

Summary of the adverse effects of penicillin